REMARKS/ARGUMENTS

Rejection under 35 USC 112

Claims 37-59 have been rejected under 35 USC 112, first paragraph for lack of enablement and written description. More specifically, the Patent Office states:

> The specification does not teach that β–amyloid epitopes can be used to inhibit the formation of β–amyloid plaques and aggregates in the brain of humans...the only thing that the specification shows is that anti-Aβ-antibodies can be made in this system using Aβ as an antigen, not that they can be used to inhibit the formation of β–amyloid plaques and aggregates in the brains of these monkeys.

Applicant respectfully traverses this rejection. Applicant's original disclosure, coupled with the state of the art at the time the instant application was filed, indicates that administration of a β-amyloid epitope would be effective in inhibiting the formation of β-amyloid aggregates and plaques. Applicant's disclosure teaches immunizing mice with a composition comprising a β–amyloid epitope. Applicant's disclosure also teaches immunizing mice with a composition comprising a plurality of β–amyloid epitopes. Immunization in each case was effective in producing antibodies that specifically bind β–amyloid in vitro. The antibody-antigen interactions would undoubtedly occur in vivo.

The binding of a large ~150 kDa antibody molecule to the much smaller ~4 kDa amyloid peptide would unavoidably greatly alter the chemical activity, biodistribution and biological actions of β–amyloid in the body. While anti-Aβ antibodies in the circulation cannot cross the blood-brain barrier to a significant extent, Applicant clearly showed that animals treated with an anti-Aβ antibody retained 10-times more labeled $A\beta_{1-40}$ in the circulation, thereby providing evidence that an Aβ antibody can sequester significant levels of Aβ and alter the equilibrium distribution of Aβ in the body (page 31, line 19 to

page 32, line 2 and Table 7). One of skill in the art would readily predict, based on the animal studies described, that immunization of a human with such a vaccine would result in similar sequestration of significant levels of β-amyloid in the circulation.

Evidence available at the time of applicant's filing indicates that lower brain β–amyloid levels can, in fact, lead to the disaggregation of plaques. It is well established that the aggregation of β-amyloid and the deposition of β-amyloid as plaques in the brain are both accelerated by an elevation in the extracellular concentration of β-amyloid (Scheuner et al., *Nature Med.* **2**: 864 (1996); Kowall et al., *Proc. Natl. Acad. Sci.* **88**: 7247 (1991)). One of ordinary skill in the art would readily predict, based on the state of the art at the time of Applicant's filing, that sequestration of significant levels of β-amyloid in the circulation would lower the extracellular concentration of amyloid and thereby prevent the formation of amyloid plaques within the human brain. Because elevated levels of full-length Aβ in the blood are associated with Alzheimer's disease (Scheuner et al., *Nature Med.* **2**: 864 (1996)), a composition whose administration results in the sequestration of amyloid in the blood would be effective in preventing and/or treating the disease with probable certainty. Any β-amyloid which is retained or drawn into the circulatory system by its interaction with antibodies would be unavailable for aggregate or plaque formation or other harmful effects in the brain. One of skill in the art would also recognize that administration of a vaccine composition comprising a β-amyloid epitope would result in the formation of immune complexes of β-amyloid with anti-β-amyloid antibodies. The resulting antibody-dependent processes, which are innate to the immune system and well known to one of skill in the art, would clear and/or destroy the β-amyloid antigen from a vaccinated individual. In light of an overwhelming

body of genetic, biochemical, and clinical evidence, it is generally accepted that β-amyloid, its aggregates and/or the plaques it forms are the underlying cause of Alzheimer's disease. Therefore, few in the art would argue that neutralizing or removing β-amyloid from the body would not have a beneficial effect in terms of preventing or curing Alzheimer's disease.

A publication printed prior to Applicant's filing date further confirms that Applicant's invention is, in fact, enabling for teaching an antibody which has the ability to inhibit the formation of β–amyloid plaques. International Application No. PCT/US98/25386 demonstrates the prophylactic efficacy of the administration of a β-amyloid peptide in treating Alzheimer's disease (page 32, line 36 to page 33, line 12). Immunizations with a β-amyloid peptide were shown to be effective in reducing the amyloid burden in mice and preventing further amyloid deposition over time relative to a control (page 41, line 13 to page 42, line 8). One of skill in the art would readily believe, based on the teachings of Applicant's disclosure and the knowledge of one of skill in the art at the time of Applicant's filing, that administration of a β-amyloid epitope would be effective in stimulating an immune response in a human, the immune response being characterized by the generation of circulating antibodies which bind specifically to the epitope present on endogenous β-amyloid in the human, the Aβ antibodies sequestering β–amyloid in the circulation, and the sequestration inhibiting the formation of β-amyloid aggregates and plaques in the brain of the human. One of skill in the art at the time the instant application was filed would readily believe, based on Applicant's disclosure and knowledge of one skilled in the art at the time of Applicant's filing, that

administration of a β-amyloid epitope or epitopes would be effective in inhibiting the formation of β-amyloid aggregates and plaques.

Applicant notes that the rejection based on the cited Schenk reference, discussed below, necessitates reliance solely on subject matter disclosed by Applicant in original Provisional Application No. 60/139,408 filed June 16, 1999. Applicant further notes that to the extent that arguments made in previously filed responsive papers included reliance on new matter added subsequent to the June 16, 1999 filing date, such arguments should not be considered by the Patent Office at this time.

Rejection under 35 USC 102

Claims 64 and 76-78 have been rejected under 35 USC 102(b) as being anticipated by Suzuki et al. The rejected claims have been cancelled, thereby obviating this rejection.

Rejections under 35 USC 103(a)

Claims 64-78 have been rejected under 35 USC 103(a) as being unpatentable over Suzuki et al. The rejected claims have been cancelled, thereby obviating this rejection.

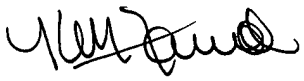
Claims 37-59 and 64-78 have been rejected under 35 USC 103(a) as being unpatentable over Schenk. Claims 39, 44, 46, 47, 52-53, 55-56, and 64-78 have been cancelled, thereby obviating the rejection of these claims. In response to the rejection of Claims 37-38, 40-42, 43 (as amended), 45, 48-51, 54, and 57-59, Applicant has attached an unexecuted Declaration under 37 CFR 1.131. Applicant has approved the

Declaration and is returning the executed Declaration to the undersigned Attorney for submission as a supplemental paper. It is respectfully submitted that this Declaration is effective to establish invention of the subject matter of the rejected claims prior to the effective date of the cited reference.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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